REMARKS

Claims 5-8 are currently pending. Claims 1-4 and 9-36 are withdrawn from consideration as being drawn to non-elected inventions. Claims 5, 6, 7, and 8 have been amended to better clarify what Applicants believe to be the invention. Support for the amendments can be found in the specification on page 36, lines 6-13; page 62, lines 16-29; and on page 5, lines 12-15. No issue of new matter is believed to be introduced by this amendment. Accordingly, claims 5-8 are currently under consideration.

The Examiner alleges that the Sequence Listing fails to meet the requirements of 37 CFR 1.821 through 1.825 because the paper copy does not match the sequence identified on page 18 of the instant application. In particular, the residue noted as $J_{Y/F/H}$ does not seem to be included in the paper copy of the sequence listing. Applicants note that a substitute Sequence Listing and Statement was provided on July 19, 2004, which corrects this error. Applicants respectfully request withdrawal of this rejection.

Claims 5-8 are rejected under 35 U.S.C. §101 because the Examiner alleges that the claimed invention is drawn to non-statutory subject matter, in particular, the Examiner has recommended to amend the claim to read on an isolated peptide. Applicants have amended the claim as suggested by the Examiner to overcome this rejection. Furthermore, claims 5-8 were rejected under 35 U.S.C. §101 because the Examiner alleges that they do not meet the specific and substantial utility requirements. Applicants have provided support for utility in the specification and also provide herewith copies of several references, attached herein as Exhibit C, that describe the significance of the bromodomains as related to their role in cancer and HIV infections. Applicants respectfully request withdrawal of this rejection.

Claims 5-8 are rejected under 35 U.S.C. §112, first paragraph for not fulfilling the written description requirement. Applicants respectfully traverse the Examiner's rejection and have also amended the claims to better clarify the invention as suggested by the Examiner. Support for the amendments can be found on page 5 lines 12-15. Thus, Applicants respectfully request withdrawal of the rejection.

Claims 5-8 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicants respectfully traverse the Examiner's rejection, and have also provided a Declaration under 37 CFR 1.132 with the inventor's curriculum vitae (attached as Exhibit A) and additional data in support of enablement (attached as Exhibit B). Thus, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 5 and 6 are rejected under 35 U.S.C. §102(b) as being anticipated by Dhalluin et al. (Nature 399: 491-96). Applicants have provided evidence as to the date of filing of the parent application, U.S. Serial Number 09/510,314, to which the present application claims priority. Since USSN 09/510,314 was filed within one year of the publication of the Applicants' own paper, Applicants assert that this rejection is moot. Thus, Applicants respectfully request withdrawal of this rejection.

Sequence Listing

The Examiner alleges that the Sequence Listing fails to meet the requirements of 37 CFR 1.821 through 1.825 because the paper copy does not match the sequence identified on page 18 of the instant application. In particular, the residue noted as $J_{Y/F/H}$ does not seem to be included in the paper copy of the sequence listing. Applicants note that a substitute Sequence Listing and Statement was provided on July 19, 2004, which corrects this error. Accordingly, the residue noted as $J_{Y/F/H}$ now reads as tyrosine, phenyalanine or histidine. Applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 5-8 under 35 U.S.C. § 101 for two reasons. The Examiner alleges that the claimed invention is drawn to non-statutory subject matter, in particular, the Examiner has recommended to amend the claim to read on an isolated peptide. Applicants have amended the claim as suggested by the Examiner to overcome this rejection.

Furthermore, claims 5-8 were rejected under 35 U.S.C. §101 because the Examiner alleges that they do not meet the specific and substantial utility requirements. The Examiner's attention is drawn to the relevant sections in the specification whereby the utility of the invention is described. In particular, on page 4, lines 3-8, Applicants describe that the invention provides support for the binding of bromodomains to the acetyl-lysine structure of proteins. Furthermore, the present invention also provides the three-dimensional structure of a bromodomain as well as the three-dimensional structure of a bromodomain-acetyl-histamine complex (the acetyl-histamine being a ligand of the bromodomain). The inventors further note that the structural information provided can be employed in methods of identifying drugs that can modulate the cellular processes that involve bromodomain-acetyl-lysine interactions. More particularly, the Applicants note
on page 4, lines 9-13:

"In a particular embodiment, the three-dimensional structural information is used in the identification and/design of an inhibitor of leukemia. In another embodiment, the three-dimensional structural information is used in the identification and/design of an inhibitor of HIV-1 infection and/or AIDS."

The Examiner's attention is further drawn to page 20, lines 27-32, continuing onto page 21, lines 1-16, wherein it states:

"Indeed, ***the bromodomain and lysine-acetylated protein interaction can now be implicated to play a causal role in the development of a number of diseases including cancers such as leukemia.*** *For example, chromatin remodeling plays a central role in the etiology of viral infection and cancer [Archer and Hodin, Curr. Opin. Genet. Biol.* ***9****:171-174 (1999); Jacobson and Pillus, Curr. Opin. Genet. Biol.* ***9****:175-184 (1999)]. Both altered histone acetylation/deacetylation and aberrant forms of chromatin-remodeling complexes are associated with human diseases. Furthermore,* ***chromosomal translocation of various cellular genes with those encoding HATs and subunits of chromatin remodeling complexes have been implicated in leukomogenesis.*** *The MOZ (monocytic leukemia zinc finger) and MLL/ALL-1 genes are frequently fused to the gene encoding the co-activator HAT CBP [Sobulo et al., Proc. Natl. Acad. Sci. USA* ***94****:8732-8737(1997)]. The resulting fusion protein MLL-CBP contains the tandem bromodomain-PHD finger-HAT domain of CBP.* ***It also has been shown that both the bromodomain and HAT domain of CBP are required for leukomogenesis, because deletion of either the bromodomain or the HAT domain results in loss of the MLL-CBP fusion protein's ability for cell transform. These results indicate that the CBP bromodomain, and more particularly, the ZA loop of the CBP bromodomain, is an excellent target for developing drugs that interfere with the bromodomain acetyl-lysine interaction that can be used in the treatment of human acute leukemia.*** *In addition, an antibody (e.g., a humanized antibody) raised specifically against a peptide from the ZA loop of the CBP bromodomain could also be effective for treating these conditions."*

Further support for the utility of the invention can be found on page 21, lines 12-15 as shown below:

"These results indicate that the CBP bromodomain, and more particularly, the ZA loop of the CBP bromodomain, is an excellent target for developing drugs that interfere with the bromodomain acetyl-lysine interaction that can be used in the treatment of human acute leukemia."

Additional support for utility can also be found on page 18, lines 4-10, whereby the inventor describes the relevance of the bromodomain in viral growth and replication, in particular, HIV expression and replication. As noted:

"In addition, as disclosed herein, the gene transactivation of HIV-1 Tat protein requires lysine-acetylation at amino acid residue 50 of Tat (see SEQ ID NO:45) by the transcription co-activator p300/CBP and the subsequent formation of a binding complex between the Tat having the acetylated lysine with P/CAF. The binding complex between P/CAF and Tat is mediated via the bromodomain of P/CAF and the acetylated lysine of Tat. Indeed, this binding is required for the gene transactivation activity of Tat and thus, for HIV-1 expression and replication."

Further support for this utility can be found on page 20, lines 11-32; on page 21, lines 1-30 and on page 73, Example 2.

Applicants further refer the Examiner to the references provided herein as Exhibit C, which provide support for the role of the bromodomain in viral replication, in particular HIV (see reference by Mujtaba et al. Molecular Cell (2002), 9:575-588) and the role of the bromodomain in tumor cell growth (see reference by Mujtaba et al. Molecular Cell (2004), 13: 251-263). More importantly, these references point out the need for identification of small molecules that block the interaction of the bromodomain with its binding partner to prevent viral replication or to induce apoptosis in tumor cells. Applicants provide herein copies of these selected references noting the utility of the bromodomains and are enclosed for the Examiner's convenience as Exhibit C.

Rejections under 35 U.S.C. § 112

Claims 5-8 are rejected under 35 U.S.C. §112, first paragraph for not fulfilling the written description requirement. In particular, the Examiner notes that the claims read on a genus of inventions comprising peptides comprising the ZA loop of a bromodomain, wherein the bromodomains have between 21-40 amino acids. However, the specification teaches that bromodomains have about 110 amino acids, not 21-40 amino acids. Accordingly, the specification does not provide written support for claims drawn to peptides comprising a bromodomain of 21-40 amino acids.

Applicants respectfully traverse the Examiner's rejection and have also amended the claims to better clarify the invention. The amended claims now recite "an isolated peptide comprising a ZA loop of a bromodomain, **said ZA loop of said bromodomain having**

between about 21 to 40 amino acids....". Accordingly, withdrawal of the rejection is respectfully requested.

Claims 5-8 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. In particular, the Examiner alleges that the claims describe a genus of peptides useful for the identification of binding partners for proteins comprising acetyl-lysines, and for the identification of compounds useful for the modulation of bromodomain/acetyl-lysine interactions. The Examiner further alleges that the application does not provide any other uses for the peptides other than in methods for such identification, nor does the application indicate what the compounds identified by such methods would be useful for. Furthermore, the Examiner alleges that there is little guidance as to either the ligands or use of the ligand binding modulators for the claimed peptides. The Examiner further alleges that the art indicates that the functions and the binding partners of the peptides are generally not known. The Examiner further alleges that the application does not provide sufficient information to enable those skilled in the art to use the claimed peptides without undue experimentation.

Support for the role of the bromodomain and its interaction with the acetyl lysine of the Tat protein in HIV can be found on page 21, lines 18-30. More importantly, the application provides evidence that acetylated lysine 50 of Tat specifically binds to the bromodomain of P/CAF. The Examiner's attention is drawn to Figures 5-10 and the results of these experiments, which are shown on page 77. This information, taken together with the fact that Tat is tightly regulated by lysine acetylation, and that HIV-1 Tat transcriptional activity is absolutely required for productive HIV viral replication is supportive of a role for this bromodomain as a drug target for blocking HIV replication in cells.

A ligand for a bromodomain is defined on page 48, lines 22-23, wherein it states:

"A compound is identified as a potential ligand if it binds to the ZA loop of the bromodomain."

As shown on page 51, lines 25-28:

"In a particular embodiment of the present invention the bromodomain-ligand complex is the Tat-P/CAF complex and the compound identified by the screen can used to prevent, retard the progression, treat and/or cure AIDS."

Applicants further assert that Example 1 on pages 52-62 supports the enablement of the ZA loop of the bromodomain binding to its ligand, which in the matter of the present application is an acetylated lysine, such as that found in acetyl-histamine.

Furthermore, agents that can inhibit the binding of the bromodomain with its binding partner/ligand can be found on page 8, lines 29-32, continuing onto page 9, lines 1-8:

"The present invention further provides agents that can inhibit the binding of a bromodomain with a protein comprising an acetyl-lysine. In one embodiment the agent is ISYGR-AcK-KRRQRR (SEQ ID NO:4). In another embodiment the agent is ARKSTGG-AcK-APRKQL (SEQ ID NO:5). In still another embodiment the agent is QSTSRHK-AcK-LMFKTE (SEQ ID NO:6). In yet another embodiment the agent is an analog of acetyl-lysine (see Figures 12 and 13). One particular analog of acetyl-lysine is acetyl-histamine. In still another embodiment the agent is an antibody that recognizes an acetyl-lysine of a protein binding partner of a bromodomain. In a preferred embodiment the agent is an antibody raised against a ZA loop of a bromodomain. These agents can be used as pharmaceuticals in compositions that contain a pharmaceutically acceptable carrier for example, or in the various drug assays of the present invention, serving as controls to demonstrate specificity."

Furthermore, Applicants have provided herein a declaration under 37 CFR 1.132 which includes additional support for compounds identified by the methods described herein. The Examiner's attention is drawn to the inventors declaration whereby compounds have been identified on the basis of the bromodomain and ZA loop sequences and coordinates provided in the instant application. These compounds, while being identified using the information provided in the current application as related to bromodomain structure, are supportive of enablement and further illustrative of the utility of the present invention.

Rejections under 35 U.S.C. § 102

Claims 5 and 6 are rejected under 35 U.S.C. 102 as being anticipated by Dhalluin et al. (Nature 399:491-96). Representative for Applicants respectfully point out to the Examiner that the rejection under 35 U.S.C. 102 is improper since this reference is a publication by the inventor of the present application and that the paper was published on June 3, 1999. The present application claims priority to USSN 09/510,314, filed on February 22, 2000, and falls within one year of the publication of the reference, thus rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

Fees

No fees are believe to be necessitated by the foregoing response. However, if this is in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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Attachments: Declaration under 1.132 with Exhibit A (curriculum vitae of Ming-Ming Zhou); Exhibit B (preprint by Zeng et al. in support of enablement); Exhibit C (references by Mujtaba et al. in support of utility)